

## **Original Research Article**

### **Comparative study of nebulization with salbutamol vs. saline solution at the acute phase of bronchiolitis of 100 children aged 1 to 23 months**

#### **Abstract**

**Introduction:** Infant bronchiolitis is the most common acute viral infection of the lower respiratory tract in children. Many pharmacological interventions have been suggested, including bronchodilators, yet the efficacy of bronchodilators in the treatment of this infection is still controversial.

**Objectives:** To evaluate the effect of nebulization of salbutamol vs. saline solution in the acute phase of bronchiolitis.

**Materials and Methods:** Using a randomized selection process, 52 infant patients received salbutamol, and 48 received a saline solution. The patients included in the study were aged 1 to 23 months and presented with their first episode of wheezing. During patient selection, we excluded children who were asthmatic or had other pulmonary issues prior to their bronchiolitis episode. Three nebulizations were performed for each patient, at one-hour intervals, after admission to the hospital. Wang's score and oxygen saturation were recorded for each patient on arrival, then at 30 minutes after each nebulization.

**Results and Conclusion:** During the treatment period (which lasts three hours), the mean Wang score decreased from 7 to 3.5, and the mean oxygen saturation increased from 92.5% to 95.6%. Statistical analysis of the data, based on a parametric statistical test of the Student type (T-test), shows that there is no significant difference between nebulization with salbutamol and those given saline solution. The evolution of the clinical scores leads to the general conclusion that we cannot recommend using salbutamol nebulization over saline solution for the treatment of bronchiolitis.

**Keywords** : bronchiolitis, bronchodilators, nebulization, Wang score.

## **Introduction**

Infant bronchiolitis is an acute viral infection of the lower respiratory tract [1, 2]. It is the most common viral infection in children and is mainly caused by the respiratory syncytial virus [3]. The condition is defined by predominantly expiratory dyspnea, and can be associated with polypnea and signs of respiratory struggle. At auscultation, there are cracklings or sibilants, sometimes audible from a distance (wheezing) [2]. Bronchiolitis is generally preceded (48 to 72 hours before) by a picture of nasopharyngitis [1, 2].

In Morocco, bronchiolitis occurs in autumn-winter as epidemics, usually starting in mid-October, peaking in December, and ending in late winter. The evolution is very variable: ranging from the mild form treated on an outpatient basis to the more serious form requiring hospitalization in the pediatric ward, or even in intensive care [2].

The treatment of bronchiolitis is currently controversial [1]: despite the number of studies reported in the literature in recent years, the therapeutic role of bronchodilators in the treatment of bronchiolitis is questioned by many practitioners. Some studies conclude that bronchodilators have no special clinical and functional efficacy [4]. Gadomski et al's extensive literature review [3] argued that, in order to answer completely the question of efficacy, there is a need for treatment trials using saline solution controls, and for randomized controlled trials with large sample size and standardized methodology. They recommended that exclusion criteria be consistently applied to exclude children with recurrent wheezing, asthma or other pulmonary disease. They surmised that widespread use of bronchodilators in bronchiolitis is likely due to the similarity between symptoms and signs of bronchiolitis and asthma.

Our study followed the above recommendation, and consisted of a double-blind study that compared the evolution of the oxygen saturation and Wang score of 100 children, half of whom received salbutamol nebulization, and the other half (the control group) received a saline solution. The aim of our study was to determine if there is a difference in efficacy between the two types of nebulization. We considered a difference of 1 point in the Wang score between the two intervention groups to be clinically significant.

## **Materials and Methods**

### **Inclusion and exclusion criteria**

The study was carried out at the pediatric pulmonology unit at the University Hospital of Rabat, during the local bronchiolitis peak season between September and January. The inclusion criteria were:

1. Age 1 to 23 months
2. First episode of wheezing
3. The patient was diagnosed with bronchiolitis

The exclusion criteria were:

1. Previous episode of wheezing
2. Pathology associated with the first episode of wheezing (sequelae of virus of infections, bronchial dilatation, heart disease, etc.)
3. Prior steroid treatment within 48 hours of admission
4. Bronchodilator treatment within 4 hours of admission
5. Respiratory rate greater than 80 cycle per minute
6. Disturbance of consciousness
7. Heart rate greater than 180 beats per minute
8. Low oxygen saturation (85% or less)

These criteria were inspired by previous studies [1,2,5-11].

### **Preparation of the nebulization solution**

As soon as an infant was selected for inclusion in the study, an assistant not otherwise involved in the study decides, based on a random draw, to fill a syringe with a salbutamol solution (0.03 ml/kg of the 0.5% solution) or with a saline solution (0.03 ml/kg of 0.9% sodium chloride solution). In both cases, 0.9% sodium chloride was added to the syringe to obtain a total solution volume of 4 ml. The person who administered the solution did not know which type of solution was in the syringe until after nebulizations were performed.

### **Administration of the nebulization solution**

The solution prepared in the syringe was administered to the patient in three nebulizations: the first at  $H_0$ , the second at  $H_1 = H_0 + 60$  minutes, and the third at  $H_2 = H_0 + 120$  minutes. Each nebulization was delivered for 10 minutes by means of an aerosol equipped with a facial mask and propelled by oxygen with a flow rate of 6 liters per minute. No other treatment was administered during the study; only nasopharyngeal obstruction was performed just before each nebulization. This approach was similar to what has been described in other work [1,2,7].

### **Follow-up**

The clinical evaluation according to the Wang score[12] and oximetric score was performed on admission and 30 minutes after each nebulization ( $H_0 + 30$  mins;  $H_1 + 30$  mins;  $H_2 + 30$  mins). The study included patients from each severity level defined by range of Wangscore:

- Score from 0 to 3: bronchiolitis with low or no severity
- Score 4 to 7: bronchiolitis of moderate severity
- Score 8 to 12: severe bronchiolitis

A favorable response to treatment was defined by the transition from one class of severity to another class of lesser severity [13].

### **Statistical Analysis**

To analyze our results, we used a T-test statistical method for comparing two proportions with large independent samples (since we have more than 30 patients)- To determine the effectiveness of a treatment method, the rate of change (ratio) of each monitored parameter (respiratory rate, wheezing, retraction score, and Wang score) was calculated between admission and discharge.

## **Results**

### **Patients at admission**

Using the same statistical design as Khanal et al [4], we determined that having 67 patients in the study would provide information with sufficient statistical significance for the comparison:

$$N = [(z_1 + z_2)^2 (O_1^2 + O_2^2)] / (u_1 - u_2)^2 \text{ where}$$

- $z_1 = 1.96$  (confidence level for  $p$  value = 0.05)
- $z_2 = 1.64$  (confidence power of 95%)
- $O_1 = O_2 = 1.7$  (standard deviation of the Wang score [5])
- $u_1 - u_2 = 1$ : we consider a difference of 1 in the Wang score as significant

To allow for some contingency, we ran the study until we gathered results for 100 patients. The characteristics of the study population at admission are reported in Table I. Of the 100 children in the study, 61 were boys and 39 were girls, and all were 1 to 23 months of age. The randomized selection resulted in almost three times as many boys as girls in the saline solution group (35 boys and 13 girls), but the number of girls and boys are the same in the salbutamol group (26 patients each). The median age in the two groups were similar (9 months vs. 8.2 months). The other epidemiological, clinical and oxymetric parameters at admission are comparable for the two groups.

**Table I : Parameters at admission (mean  $\pm$  stdv)**

	Salbutamol	Saline solution
Number of patients	52	48
Sex (F/M)	26/26	13/35
Age (months)	9.0 $\pm$ 6.1	8.2 $\pm$ 5.72

### **Nebulization of salbutamol**

Tables II summarises the evolution of the means of the scores during the treatment with salbutamol. In addition to the Wang score, the table shows the respiratory rate score, the sibilant score, and the retraction score. The respiratory rate score is defined as 0 for a respiratory rate less than 30 breaths/min; 1 for a rate between 31 to 45; 2 for a rate between 46 to 60; and 3 for a respiratory rate greater than 61 breaths/min. The retraction score is defined as: 0 for Normal; 1 for intercostal; 2 for tracheostomal, and 3 for Severe with nasal flaring irritability, lethargy and poor feeding.

The table shows that all four scores improved steadily from admission to the last nebulisation with salbutamol. The oxygen saturation increased. These changes correspond to an improvement in the children's condition throughout the treatment.

**Table II: Evolution of the patient group nebulized with salbutamol (mean  $\pm$  stdv)**

	Admission	H <sub>0</sub> +30 mins	H <sub>0</sub> +90 mins	H <sub>0</sub> +150 mins
Respiratory rate score	2.4 $\pm$ 0.5	2.4 $\pm$ 0,5	1.8 $\pm$ 0,5	1.3 $\pm$ 0,4
Sibilant score	2.0 $\pm$ 0.3	1.8 $\pm$ 0,4	1.2 $\pm$ 0,4	1.0 $\pm$ 0,2
Retractionscore	2.2 $\pm$ 0.4	2.1 $\pm$ 0,4	1.5 $\pm$ 0,5	1.1 $\pm$ 0,4
Wang score	7.0 $\pm$ 1.5	6.6 $\pm$ 1.7	4.8 $\pm$ 1.6	3.4 $\pm$ 0.9
Oxygen saturation (%)	92.3 $\pm$ 2.2	92.8 $\pm$ 2.4	94.4 $\pm$ 1.6	95.6 $\pm$ 1.2

### **Nebulization of the saline solution**

Tables III summarises the evolution of the means of the scores during the treatment with the saline. The table shows that all four scores improved steadily from admission to the last nebulisation. The oxygen saturation increased. These changes correspond to an improvement in the children's condition throughout the treatment.

Figures I to V shows the evolution of the four scores and the oxygen saturation percent for the two treatments. Visually, we observe that both treatments result in similar rates of improvement from admission to end of treatment.

**Table III: Evolution of the patient group nebulized with saline solution (mean  $\pm$  stdv)**

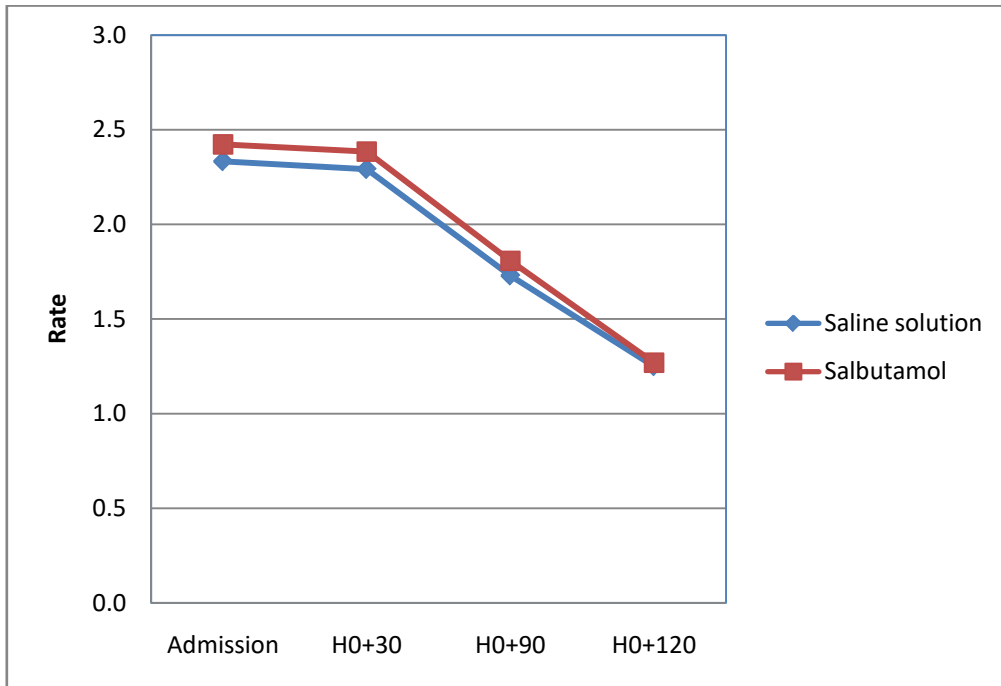
	Admission	H <sub>0</sub> +30 mins	H <sub>0</sub> +90 mins	H <sub>0</sub> +150 mins
Respiratory rate	2.3 $\pm$ 0.5	2.3 $\pm$ 0.5	1.7 $\pm$ 0.5	1.3 $\pm$ 0.5
Sibilant score	2.0 $\pm$ 0.3	1.8 $\pm$ 0.5	1.3 $\pm$ 0.4	1.0 $\pm$ 0.3
Retraction score	2.2 $\pm$ 0.4	2.1 $\pm$ 0.4	1.4 $\pm$ 0.5	1.1 $\pm$ 0.3
Wang score	6.7 $\pm$ 1.7	6.5 $\pm$ 1.5	4.6 $\pm$ 1.1	3.4 $\pm$ 0.8
Oxygen saturation (%)	92.7 $\pm$ 2.1	93.0 $\pm$ 2.1	94.7 $\pm$ 1.7	95.8 $\pm$ 1.2

**Table IV: Change in each monitored parameter between admission and discharge and corresponding p-values.**

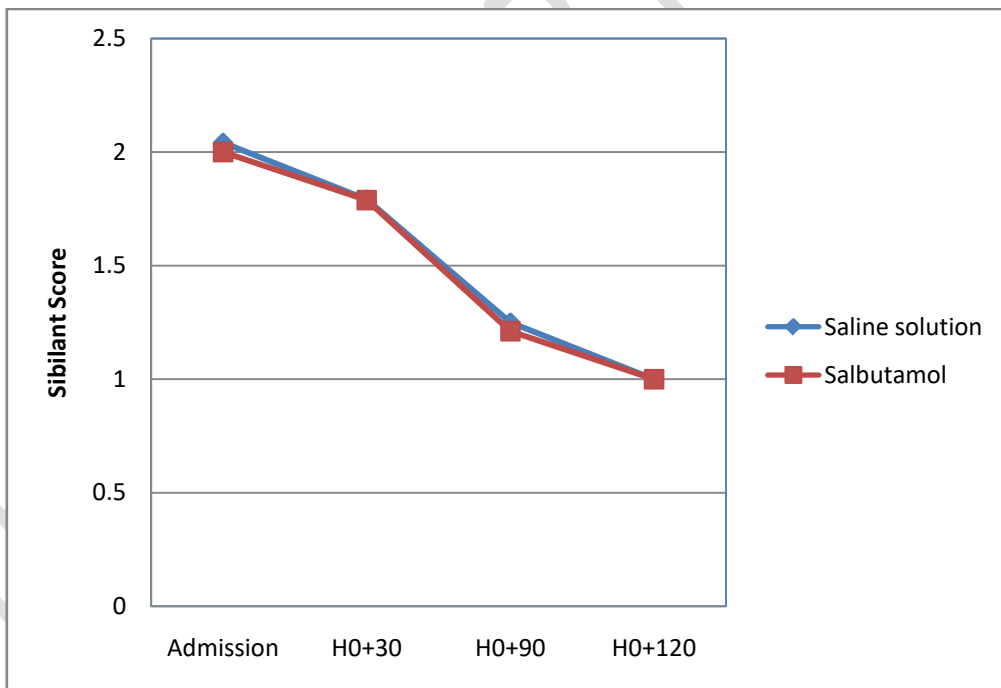
Parameter	Ratio		Z	p-value
	Saline solution	Salbutamol		
Respiratory rate score	53.57%	52.38%	0.119	0.906
Sibilant score	48.98%	50.00%	0.102	0.919
Retraction score	50.48%	51.33%	0.085	0.933
Wang score	50.16%	48.90%	0.125	0.901

The smallest p-value statistic corresponding to these ratios is p-value = 0.901. This value being higher than the standard value of the risk threshold = 0.05, confirming the hypothesis that the two treatments cannot be differentiated.

**FIGURE 1 : RESPIRATORY RATE SCORE**

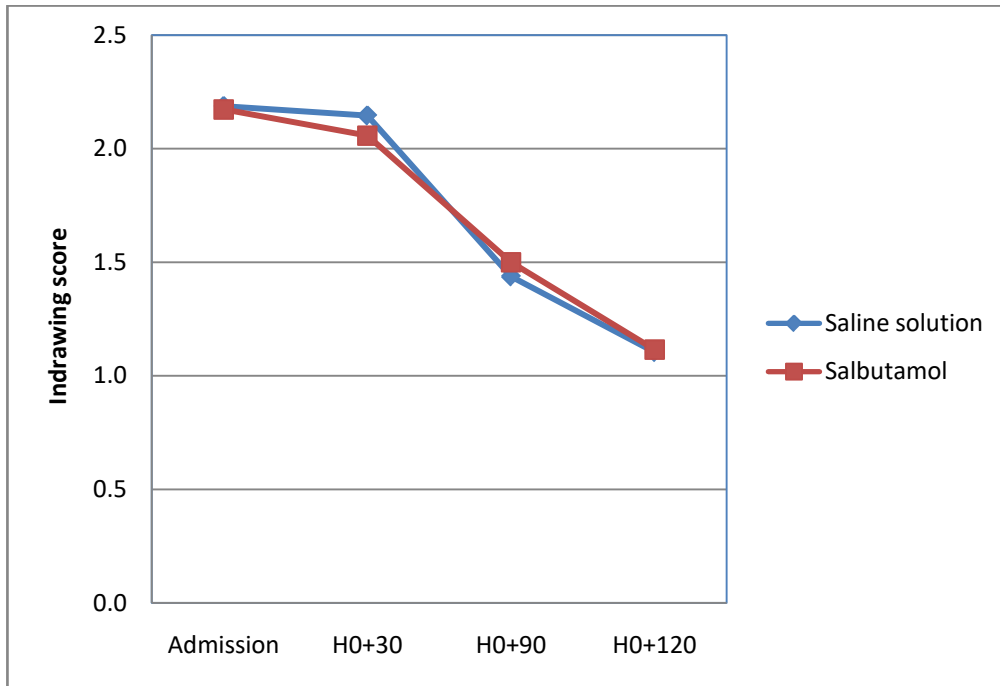


**FIGURE 2 : SIBILANT SCORE**





**FIGURE 3 : RETRACTIONSCORE**



**FIGURE 4 : WANG SCORE**

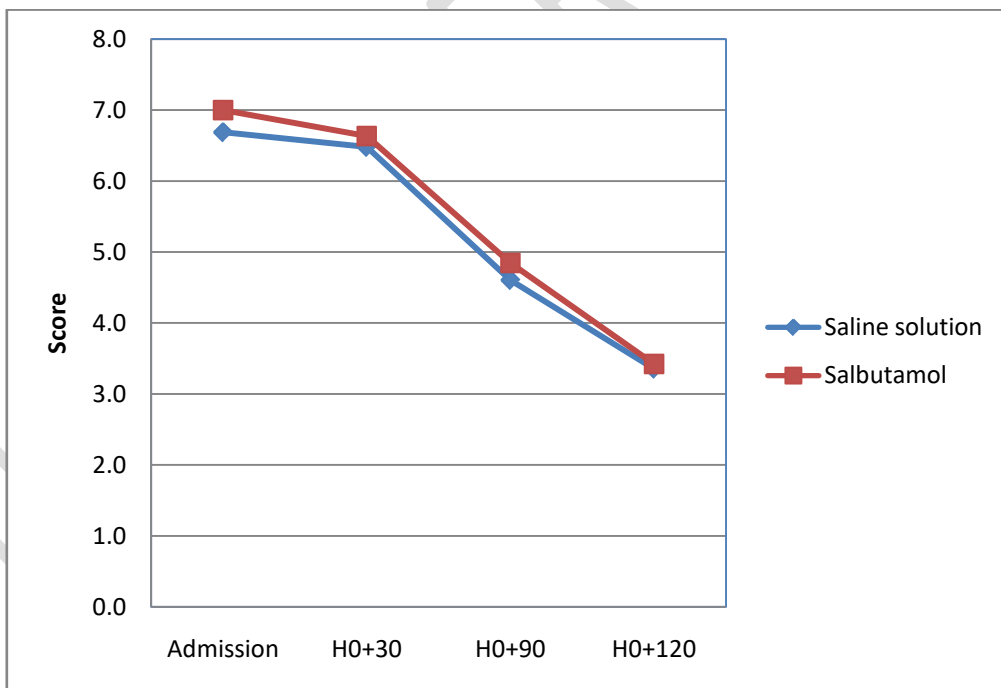
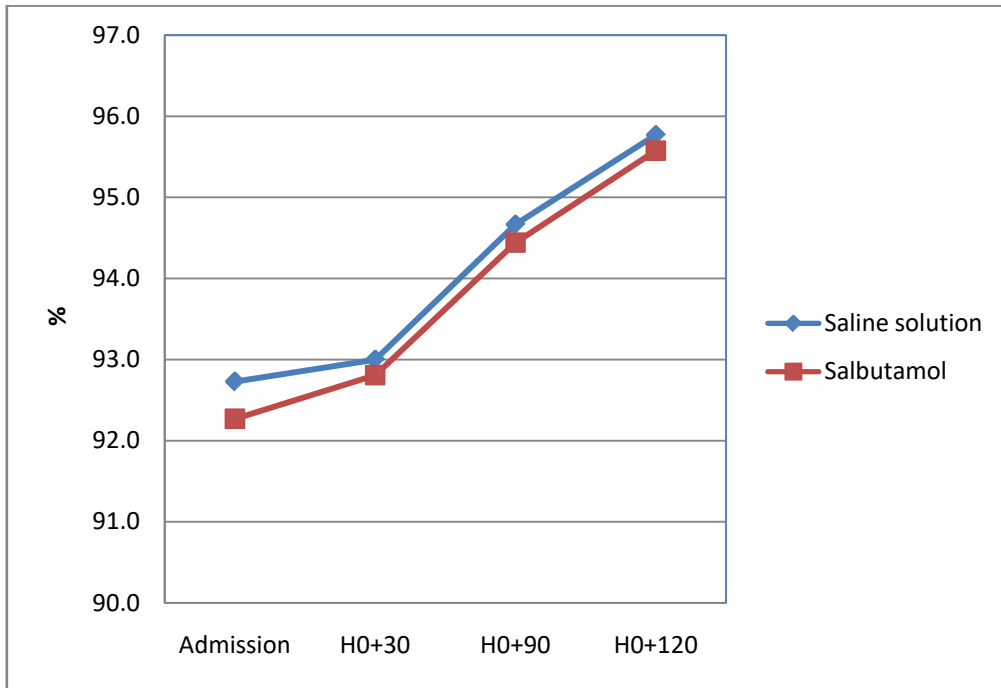


FIGURE 5 : OXYGEN SATURATION (%)



UNDER PEER REVIEW

## **Discussion**

Our study was designed to minimize the biases and limitations described in Gadomski et al's extensive literature review [3]. The sample size was significant (100 infants), and the strict inclusion and exclusion criteria were used to minimize possible confounding effects. Blinding was maintained each patient from admission to release.

Bronchodilators, which are known to reverse bronchoconstriction induced by asthma, have not proven to be as effective for children with bronchiolitis. Bronchodilators such as albuterol or salbutamol have not improved oxygen saturation or any of the Wang Score parameters [4, 12]. This could be because the pulmonary beta-agonist receptor sites of children appear inadequate, and because the potential effectiveness of  $\beta_2$ -adrenergic agonists is limited by the smooth muscles of their bronchiolar walls. This is confirmed by the results of our study. Visually, the graphs shown in the Results section, as well as the p-values shown in Table IV, show that salbutamol nebulization has no significant advantage over placebo in improving oxygen saturation or Wang's score. For both groups, there is gradual improvement in all scores and the effect seemed to be more pronounced after the second session of nebulization at 30 min. But there is no significant difference in the mean change in each score between the two groups.

Given the adverse side effects and the expense associated with these treatments, bronchodilators are not effective in the routine management of bronchiolitis. As asthmatic children are known to respond to bronchodilators, their exclusion from our study prevented a false increase in the apparent level of efficacy of bronchodilators in patients with bronchiolitis. This result is consistent with the results of other studies [3, 12].

## **Conclusion**

The results show that salbutamol nebulization is not more effective than saline solutions in the routine management of bronchiolitis. Therefore the use of bronchodilators in the management of the first bronchiolitis cannot be recommended.

## **Ethical approval**

The Ethics Committee has been informed that the study is about a comparative evaluation of two common treatment methods.

## **Consent**

Informed verbal consent was taken from the parents of all children.

UNDER PEER REVIEW

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